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(REDACTED)

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

GRACEWAY PHARMACEUTICALS, LLC AND 3M INNOVATIVE PROPERTIES COMPANY Plaintiffs v. NYCOMED US INC., Defendant.	Civil Action No. 2:10cv937 (WJM)(MF)

DEFENDANT NYCOMED US INC.'S MOTION FOR SUMMARY JUDGMENT OF INVALIDITY OF U.S. PATENT NO. 7,655,672 FOR INDEFINITENESS

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Federal Cases

Federal Statutes

I. INTRODUCTION

Defendant Nycomed US Inc. ("Nycomed") moves for summary judgment that all asserted claims of U.S. Patent No. 7,655,672 ("the '672 patent") are invalid as indefinite under 35 U.S.C. § 112, ¶ 2, pursuant to Rule 56 of the Federal Rules of Civil Procedure, Local Civil Rules 7.1 and 56.1, and this Court's Scheduling Order dated February 2, 2011 (D.I. 212).

Each of the independent claims in the '672 patent recites the phrases "at least about 80% oleic acid" and "imiquimod-related impurities." Neither phrase is a term of art with a known meaning, and the intrinsic evidence fails to inform a person of ordinary skill in the art what either is supposed to mean. Under these circumstances, the Federal Circuit law makes clear that both of these terms are indefinite under 35 U.S.C. § 112, ¶ 2. Accordingly, independent claims 1, 7, and 13 (and claims 2-6, 8-12, and 14-20, which depend on these claims) are invalid.[1]

II. BACKGROUND

The '672 patent claims pharmaceutical creams for topical application comprising imiquimod and an "oleic acid component." (i.e., a preformulation source or composition of matter containing oleic acid (which may include other fatty acids in addition to oleic acid)). The claims also recite various stability requirements for those creams – that is, how long those creams must retain certain claimed characteristics over time under various storage conditions. These stability requirements place limitations on the amount of so-called "imiquimod-related impurities" that can be found in the cream.

According to the specification, the claimed creams are supposedly more stable than other prior art creams that did not utilize the claimed "oleic acid component," specifically, those prior

[1] Because this motion addresses terms that are present in each claim of the '672 patent, a finding that either term is indefinite would render all of the claims at issue invalid and thereby be case-dispositive.

art creams that used an "oleic acid component" containing higher amounts of "polar impurities." Duh Decl., Ex. A ('672 patent) at 1:66-2:9, 7:56-62. To achieve this allegedly improved stability, the claims (not surprisingly) require that the oleic acid component must meet certain requirements regarding its purity, including maximum amounts of "polar impurities" and maximum peroxide values as determined "at or prior to formulation of said pharmaceutical cream." The claims also require that the "oleic acid component at or prior to formulation of said pharmaceutical cream contains at least about 80% oleic acid by weight as a fatty acid."

Oleic acid is a fatty acid. A fatty acid is a long-chain monocarboxylic acid. Declaration of Christian Schoneich, Ph.D. ("Schoneich Decl."), ¶ 13. Oleic acid is used in topical pharmaceutical formulations because it helps drugs penetrate the skin more effectively. Schoneich Decl., ¶ 14. Oleic acid has long been known as one of the most effective solubilizing agents for imiquimod, which is highly insoluble in aqueous systems. *See* Duh Decl., Ex. U (Chollet et al., "Development of a Topically Active Imiquimod Formulation," *Pharmaceutical Development and Technology*, 4(1), 35-43 (1999)) at 38, Table 1.

Imiquimod is a compound that acts as an immune response modifier, meaning that it stimulates some aspects of the immune system while suppressing others. Duh Decl., Ex. A ('672 patent) at 1:21-25. Imiquimod is used to treat keratosis, basal cell carcinoma, and anogenital warts associated with human papillomavirus. *Id.* at 1:40-43.

III. LEGAL PRINCIPLES

A. Legal standard for summary judgment

Summary judgment should be granted when there are no genuine issues of material fact and the moving party is entitled to judgment as a matter of law. Fed. R. Civ. P. 56(c); *Celotex Corp. v. Catrett*, 477 U.S. 317, 322 (1986). "Summary judgment is as appropriate in a patent

case as it is in any other case." *Desper Prods., Inc. v. QSound Labs, Inc.*, 157 F.3d 1325, 1332 (Fed. Cir. 1998) (internal quotation marks omitted).

B. Indefiniteness

The analysis of indefiniteness under section 35 U.S.C. § 112, ¶ 2 is a question of law that is "drawn from the court's performance of its duty as the construer of patent claims." *Default Proof Credit Card Sys., Inc. v. Home Depot U.S.A.*, 412 F.3d 1291, 1298 (Fed. Cir. 2005) (quoting *Atmel Corp. v. Info. Storage Devices*, 198 F.3d 1374, 1378 (Fed. Cir. 1999)). As such, indefiniteness is an issue suitable for summary judgment. *See IPXL Holdings, LLC v. Amazon.com, Inc.*, 430 F.3d 1377, 1384 (Fed. Cir. 2005) (affirming summary judgment that the patent claim was invalid for indefiniteness).

Every patent specification must conclude with one or more claims "particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." 35 U.S.C. § 112, ¶ 2. "Because claims delineate the patentee's right to exclude, the patent statute requires that the scope of the claims be sufficiently definite to inform the public of the bounds of the protected invention, i.e., what subject matter is covered by the exclusive rights of the patent." *Halliburton Energy Servs., Inc. v. M-I, LLC*, 514 F.3d 1244, 1249 (Fed. Cir. 2008). In this regard, "[i]t is the applicants' burden to precisely define the invention, not the PTO's," because section 112, ¶ 2 "puts the burden of precise claim drafting squarely on the applicant." *In re Morris*, 127 F.3d 1048, 1056 (Fed. Cir. 1997).

To comply with the definiteness requirement under § 112, ¶ 2, the skilled artisan must be able to discern "the boundaries of the claim based on the claim language, the specification, and the prosecution history, as well as her knowledge of the relevant art area." *Halliburton*, 514 F.3d at 1249-50. A claim is indefinite where "a person of ordinary skill in the art could not determine the bounds of the claims, i.e., the claims were insolubly ambiguous." *Id.* at 1249. "Even if a

claim term's definition can be reduced to words, the claim is still indefinite if a person of ordinary skill in the art cannot translate the definition into meaningfully precise claim scope." *Id.* at 1251. Extrinsic evidence in the form of expert testimony cannot provide the required definiteness absent the expert identifying parameters by which the metes and bounds of the invention can be delineated. *Datamize, LLC v. Plumtree Software, Inc.*, 417 F.3d 1342, 1353-1355 (Fed. Cir. 2005). In short, "[t]he scope of claim language cannot depend solely on the unrestrained, subjective opinion of a particular individual purportedly practicing the invention." *Id*. at 1350 ("[A] claim term, to be definite, requires an objective anchor.").

Claims reciting compounds are indefinite when "the claimed compounds cannot be identified by testing and [when] one skilled in the art could not determine whether a given compound was within the scope of the claims." *Morton Int'l, Inc. v. Cardinal Chem. Co.*, 5 F.3d 1464, 1470 (Fed. Cir. 1993). If "the evidence shows that the claims at issue . . . are not sufficiently precise to permit a potential competitor to determine whether or not he is infringing, [then] the claims are invalid for failure to satisfy the 'definiteness' requirement of section 112, second paragraph." *Id.* (citing *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1218, (Fed. Cir. 1991)). *See also Star Scientific Inc. v. R.J. Reynolds Tobacco Co.*, 537 F.3d 1357, 1373 n.12 (Fed. Cir. 2008) ("[A] claim is indefinite if a skilled artisan cannot determine if an accused product infringes or not . . . . ").

IV. THE PHRASE "IMIQUIMOD-RELATED IMPURITIES" IS INDEFINITE

Each of the independent claims of the '672 patent contains the term "imiquimod-related impurities." Duh Decl., Ex. A ('672 patent), claims 1, 7, 13. In the context of the '672 patent, that term is indefinite, rendering each of the independent claims invalid.

A. The term "imiquimod-related impurities" is neither a term of art nor defined by the intrinsic evidence.

The term "imiquimod-related impurities" is not a term of art and has no general meaning to a person of ordinary skill in the art. Schoneich Decl., ¶ 30. Further, none of the claims, the specification, or the prosecution history sheds any light on the meaning of the term "imiquimod-related impurities" in the context of the '672 patent. Schoneich Decl., ¶¶ 31-32. Indeed, this term is not mentioned (let alone defined) in the specification and was not included in the claims as originally filed. It is a completely undefined term, and a person of skill in the art is provided no guidance whatsoever as to how "related" to imiquimod any "impurit[y]" needs to be to fall within the scope of the claim.

1. <u>The term "imiquimod-related impurities" has no general meaning to a person of ordinary skill in the art.</u>

The term "imiquimod-related impurities" was not a known term of art to persons of ordinary skill in the art at the time of the invention described and claimed in the '672 patent. Schoneich Decl., ¶ 30. Rather, a person of ordinary skill in the art would readily understand that there are several ways in which "impurities" may be "related" to imiquimod. *Id.*, ¶ 33. For example, imiquimod degradation products, compounds formed from the degradation of imiquimod degradation products, compounds left over from the manufacturing process, compounds from the starting materials used to make imiquimod, compounds that leached from or through the packaging into the imiquimod, and any other non-imiquimod compound found in the presence of imiquimod all ***may*** be considered by those of skill in the art to be "impurities"

that are "related" to imiquimod. *Id.* Yet it is entirely unclear which would qualify as the claimed "imiquimod-related impurities" and which would not, as that term is used in the '672 patent.[2]

Focusing first only on those impurities that could be considered degradation products, imiquimod may be degraded by several different mechanisms, forming many different degradants. Schöneich Decl., ¶¶ 18-23, 35-40. These degradation products may themselves degrade further through multiple processes. *Id.* at ¶¶ 19-20, 22, 40. Any compound formed from the degradation of imiquimod could potentially be considered by those of skill in the art as "imiquimod-related," including these secondary degradation products. *Id.* at ¶¶ 33-44. But it is entirely unclear whether some or all of these degradation products should be considered to be "imiquimod-related impurities" as that term is used in the '672 patent. *Id.*

Other components of the claimed formulation may also be degraded by several different mechanisms, and may form degradants that are identical to the degradants formed from imiquimod. *See, e.g.*, Schöneich Decl., ¶¶ 56-58. For example, BHT can react with oleic acid-derived hydroperoxides to form a series of products including hydroxyl-substituted products, which are identical to some imiquimod degradation products. *Id.* It is impossible to distinguish degradation products formed as a result of the break down of imiquimod from these other

[2] Although it is not direct evidence of indefiniteness, it is worth noting that the claims and Plaintiffs' proposed construction are scientifically flawed, given that many of these compounds do not absorb at 308 nm. Molecules in a solution can be separated using a technique called high-performance liquid chromatography ("HPLC"), and then measured using various detection devices. Schöneich Decl., ¶¶ 24-25. For example, concentrations of compounds can be determined by transmitting ultraviolet ("UV") light through the sample after separation by HPLC, and measuring the amount of light absorbed by the sample. *Id.* at ¶ 26. The concentration of the compounds is proportional to their absorbance. *Id.* This method will only work, however, for compounds that absorb UV light, and even then it will only work if the proper wavelength of UV light is selected (the UV spectrum of light is considered to have wavelengths in the range of 10 nm to 400 nm). *Id.* at ¶ 26. Therefore, a UV detector set at 308 nm will not detect compounds that do not absorb UV light at 308 nm. *Id.*

identical degradation products because they are chemically identical, and they are mixed together in the pharmaceutical cream. Schöneich Decl., ¶¶ 54, 56-58. Accordingly, it would be impossible for one of ordinary skill in the art to determine whether and when such products would qualify as the claimed "imiquimod-related impurities," in turn making it impossible to determine if any particular cream infringes the asserted claims of the '672 patent. "[A] claim is indefinite if a skilled artisan cannot determine if an accused product infringes or not." *Star Scientific*, 537 F.3d at 1373 n.12.

Further, a person of ordinary skill in the art would understand that "imiquimod-related" could be far broader than just impurities that result directly from the breakdown of imiquimod, or those that are identical to such degradants. Imiquimod contains numerous residual materials, including solvents and heavy metals. Schöneich Decl., ¶¶ 41, 46. Some of these same materials may be found in oleic acid or other components of the pharmaceutical cream. Declaration of Russell O. Potts, Ph.D. ("Potts Decl."), ¶ 10. Once the oleic acid and imiquimod are mixed together, it is impossible to determine which molecules of the residual material came from the imiquimod, and which came from the oleic acid. *See, e.g.*, Schöneich Decl., ¶¶ 54, 58. This further makes it impossible for one of ordinary skill in the art to determine if any particular impurity is "imiquimod-related" and if any particular cream infringes the asserted claims of the '672 patent. *See Morton*, 5 F.3d at 1470 (If "the evidence shows that the claims at issue . . . are not sufficiently precise to permit a potential competitor to determine whether or not he is infringing, [then] the claims are invalid for failure to satisfy the 'definiteness' requirement of section 112, second paragraph."). This impossibility renders the claims of the '672 patent indefinite.

2. The claims, specification, and prosecution history all fail to provide meaningfully precise claim scope for this term.

The phrase "imiquimod-related impurities" appears nowhere in the '672 patent other than in the claims, which merely specify the amount of so-called "imiquimod-related impurities" in the claimed pharmaceutical cream. Duh Decl., Ex. A ('672 patent), claims 1, 7, 13. The specification does not mention, let alone define, "imiquimod-related impurities," and there is no teaching, suggestion, or disclosure of what this term means. The specification refers only to "polar impurities" and "impurities" generally. In short, the patent provides absolutely no guidance regarding the meaning of this term, including what constitutes the claimed "impurities," what particular molecules found in an imiquimod formulation are "related" to imiquimod, how to determine whether any particular molecules are "related" to imiquimod, and how "related" to imiquimod a molecule must be in order to qualify as the claimed "imiquimod-related impurities."

The specification describes a "Test Method" used "to determine the amount of ***impurities*** in ***cream formulations containing oleic acid***." Duh Decl., Ex. A ('672 patent) at 13:47-51 (emphases added). This Test Method is not described as being specific to imiquimod, let alone to so-called "imiquimod-related impurities"; instead, it is described as determining the amount of "impurities" in "cream formulations containing oleic acid." *Id.* According to the patent, "[s]amples were analyzed using the test method described above for impurities . . . . The results are shown in Table 2 . . . . " *Id.* at 15:1-4. Table 2 is set forth below:

TABLE 2

	Impurities (% wt/wt)			
Timepoint	A	B	C	D
[1]Initial - top	0.09	0.08	0.02	0.03
[2]2 months - top	0.25	0.32	0.07	0.09
[2]2 months - bottom	0.33	0.30	0.04	0.15
[3]4 months - top	0.42	0.76	0.18	0.15
[3]4 months - bottom	0.46	0.56	0.04	0.29
[4]6 months - top	0.81	0.30	0.07	0.14
[4]6 months - bottom	0.49	0.29	0.04	0.07

Id. at 15:9-19. Nowhere does the patent refer to the alleged impurities in Table 2 as "imiquimod-related impurities." Indeed, as originally presented to the Patent Office, the patent claims referred to the alleged impurities in Table 2 as "polar impurities," further confirming that the meaning of the term "imiquimod-related impurities" was not clear even to the inventors themselves.

3. The original claims referred to what the issued claims call "imiquimod-related impurities" as "polar impurities"

The term "imiquimod-related impurities" did not appear in the original claims (or application) as filed. Duh Decl., Ex. B (12/12/08 Specification & Claims) at 24-28 (original claims 1-28). Nor did this term appear in the claims added in the Applicants' December 12, 2008 submission to the Patent Office. Ex. C (12/12/08 First Preliminary Amendment) at 2-5 (additional claims 29-46). Instead, this term appeared for the very first time later in the prosecution in claim amendments made by Applicants to overcome prior art objections.

In the December 12, 2008 submission to the Patent Office, the Applicants presented and discussed claims that recited that the impurities that were measured and reported in Table 2 were not "imiquimod-related impurities" at all but rather "polar impurities," even though Plaintiffs now argue that those impurities are the claimed "imiquimod-related impurities." In particular, independent claim 29 recited:

> wherein said pharmaceutical formulation contains ***polar impurities*** in an amount of no more than 0.03% wt./wt. after storage at ambient conditions for about 15 days

Independent claim 35 recited:

> wherein the pharmaceutical formulation contains ***polar impurities*** in an amount of no more than about 0.15% wt./wt. after storage for at least about 2 months at about 40 C and about 75% humidity

And independent claim 41 recited:

> wherein the pharmaceutical formulation contains ***polar impurities*** in an amount of no more than about 0.29% wt./wt. after storage for at least about 2 months at about 40 C and about 75% humidity

Duh Decl. Ex. C (12/12/08 First Preliminary Amendment) at 2-4 (emphases added).

These three claims eventually issued as independent claims 1, 7, and 13 of the '672 patent. As issued, these claims now refer to what the claims originally called "polar impurities" as "imiquimod-related impurities." In particular, claim 1 of the '672 patent recites:

> wherein said pharmaceutical cream contains ***imiquimod-related impurities*** in an amount of no more than about 0.03% wt./wt. after storage of said pharmaceutical cream at ambient conditions for about 15 days

Claim 7 of the '672 patent recites:

> wherein said pharmaceutical cream contains ***imiquimod-related impurities*** in an amount of no more than about 0.15% wt./wt. after storage of said pharmaceutical cream for at least about 2 months at about 40°C and about 75% humidity

And claim 13 of the '672 patent recites:

> wherein said pharmaceutical cream contains ***imiquimod-related impurities*** in an amount of no more than about 0.29% wt./wt. after storage for at least about 4 months at about 40°C and about 75% humidity

Duh Decl., Ex. A ('672 patent), claims 1, 7, 13. The fact that the claims originally referred to the substances measured in Table 2 as "polar impurities" found in the "formulation" – not the so-called "imiquimod-related impurities" as now argued by Plaintiffs – underscores the ambiguity of this term.

Moreover, contemporaneous with the submission of these claims, Applicants submitted an Accelerated Examination Support Document in support of a Petition to Make Special Under 37 CFR 1.102(d).[3] Nowhere does this document refer to (or otherwise discuss) "imiquimod-related impurities." Instead, in the section entitled "Detailed Explanation of Patentability," Applicants again characterized the substances allegedly measured in Table 2 as "polar impurities":

> Furthermore, through utilization of an oleic acid component containing a very low amount of polar impurities, the subsequent formation of ***impurities*** in IRM ***formulations*** is significantly reduced as compared to other IRM formulations comprising compendial grades of oleic acid after both the initial measurement (i.e., its measurement when initially formulated) and under accelerated conditions (when stored for at least 2 and 4 months at 40° C and 75% relative humidity), resulting in an increased formulation shelf life . . . ***As such, all of the references cited fail to at least teach or suggest a pharmaceutical formulation for increasing the stability . . . but which contains low levels of polar impurities after ambient or accelerated storage conditions, as required in claims 1, 7, and 13.***

Duh Decl., Ex. D (12/12/08 Accelerated Examination Support Document) at 15 (emphases added).

In the section entitled "Concise Statement of Utility," Applicants further represented that "[t]he invention as claimed has further utility in that it provides pharmaceutical ***formulations*** of Imiquimod with lower levels of ***polar impurities*** and, thus greater stability as described in page 11, line 24 through page 12, line 14." *Id.* at 15-16 (emphases added). The pages cited by Applicants correspond to col. 7, line 39 to col. 8, line 4 of the '672 patent, which states in part that:

> [T]he subsequent formation of impurities in [the claimed] IRM formulations is significantly reduced as compared to other IRM formulations comprising

[3] A Petition to Make Special is formal request submitted to the Patent Office asking that a patent application be examined ahead of the other pending applications in the same technological art.

> compendial grades of oleic acid after both the initial measurement (i.e., its measurement when initially formulated) and under accelerated conditions (when stored for at least 4 months at 40º C and 75% relative humidity), resulting in an increased formulation shelf life.

Duh Decl., Ex. A ('672 patent) at 7:64-8:4.

In the section entitled "Showing of Support under 35 USC 112, First Paragraph," Applicants stated:

> Support also is provided in the Examples section wherein Table 2 on page 23 of the application clearly demonstrates that the use of SUPER REFINED oleic acid, as opposed to unrefined oleic acid, in formulations of Imiquimod result in significantly lower levels of ***impurities***, and consequently greater stability of such formulations.

Duh Decl., Ex. D (12/12/08 Accelerated Examination Support Document) at 16 (emphasis added). Thus, Applicants repeatedly represented to the Patent Office that the alleged impurities measured in Table 2 were what they believed to be "polar impurities," not the later-claimed "imiquimod-related impurities," whatever those might be.

On March 6, 2009, the Examiner rejected all pending claims as obvious. Of relevance, the Examiner stated: "One would be motivated to include the Super Refined Oleic Acid because it is known to have less polar impurities . . . . Therefore, if one of skill in the art . . . wanted to ensure that there was a low amount of polar impurities and high stability of the overall product would occur, one would be led to use Super Refined Oleic Acid NF . . . . " Duh Decl. Ex. E (3/6/09 Non-Final Rejection) at 3.

In response, on April 6, 2009, without any explanation, Applicants amended the claims to change all prior instances of "polar impurities" to "imiquimod-related impurities." Duh Decl., Ex. F (4/6/09 Amendment & Response to Office Action) at 2, 4-6 (amending claims 29, 35, and 41). Applicants then characterized their invention for the first time as follows:

> More specifically, and as claimed in independent claims 29, 35, and 41, the pharmaceutical formulations contain lower amounts of ***imiquimod-related impurities*** when stored under ambient or accelerated conditions . . . .

Id. at 13 (emphasis in original). Applicants argued that the claims were not obvious because a person of ordinary skill in the art would not expect that using a purer form of oleic acid with imiquimod would result in lower amounts of so-called "***imiquimod-related impurities***," even if it would apparently result in lower amounts of "polar impurities" as they had previously argued and represented to the Patent Office. Duh Decl., Ex. F (4/6/09 Amendment & Response to Office Action) at 16-26. Yet the so-called "imiquimod-related impurities" referred to precisely the same substances in Table 2 that were previously called "polar impurities" by Applicants in the earlier (rejected) claims. Applicants' material confusion over the proper characterization of the substances that were supposedly measured and reported in Table 2 highlights the indefiniteness of the term "imiquimod-related impurities" (and only exacerbates the ambiguities of this term to a person of ordinary skill in the art).

4. <u>The alleged "support" provided by Applicants during prosecution only emphasizes the ambiguity of the term "imiquimod-related impurities."</u>

As discussed above, Applicants introduced the term "imiquimod-related impurities" for the very first time in an Amendment dated April 6, 2009. Duh Decl., Ex. F (4/6/09 Amendment & Response to Office Action) at 2-4, 6. In support, Applicants cited paragraphs 66, 119, and 123 of the published application.[4] Duh Decl., Ex. F (4/6/09 Amendment) at 9. These paragraphs are reproduced below:

> [0066] Unless otherwise indicated, all numbers expressing quantities, ratios, and numerical properties of ingredients, reaction conditions, and so forth used in the

[4] These paragraphs correspond to col. 7:19-23, col. 13:24-32, and col. 13:52-62, respectively, of the '672 patent.

> specification and claims are to be understood as being modified in all instances by the term "about."
>
> [0119] In one embodiment, the formulations can be applied to the surface of skin for treatment of actinic keratosis (AK). Actinic keratosis are premalignant lesions considered biologically to be either carcinoma in-situ or squamous intraepidermal neoplasia. AK is the most frequent epidermal tumor and is induced by ultraviolet (UV) radiation, typically from sunlight. Because of its precancerous nature, AK may be considered the most important manifestation of sun-induced skin damage.
>
> [0123] HPLC parameters: Analytical column: ZORBAX RX C8, 5 micron particle, 15.0.times.0.46 cm, (available from Agilent Technologies, Wilmington, Del., USA); Detector: UV at 308 nm; Mobile phase: gradient mixture of aqueous ammonium phosphate buffer (prepared by combining 5.1 mL of ortho-phosphoric acid with 985 mL of water and then adjusting to pH 2.5 with concentrated ammonium hydroxide) and acetonitrile; Gradient: start run at 10% acetonitrile, zero initial hold time, then linear gradient to 70% acetonitrile over 15 minutes, zero final hold time; Flow rate: 2.0 mL/minute; Injection volume: 200 .mu.L; Run time: 15 minutes.

Duh Decl., Ex. L (U.S. Publication No. 20070123558), ¶¶ [0066], [0119], [0123].

None of these paragraphs even mentions, let alone defines, "imiquimod-related impurities." Paragraph 66 discusses the term "about," paragraph 119 discusses actinic keratinosis, and paragraph 123 describes an HPLC method which, according to paragraph 122, can be "used to determine the amount of ***impurities*** in ***cream formulations containing oleic acid***." Duh Decl., Ex. A ('672 patent) at 13:50-51 (emphases added). If anything, these paragraphs only add to the term's ambiguity, as they do nothing to explain what type of "impurities" are to be measured.

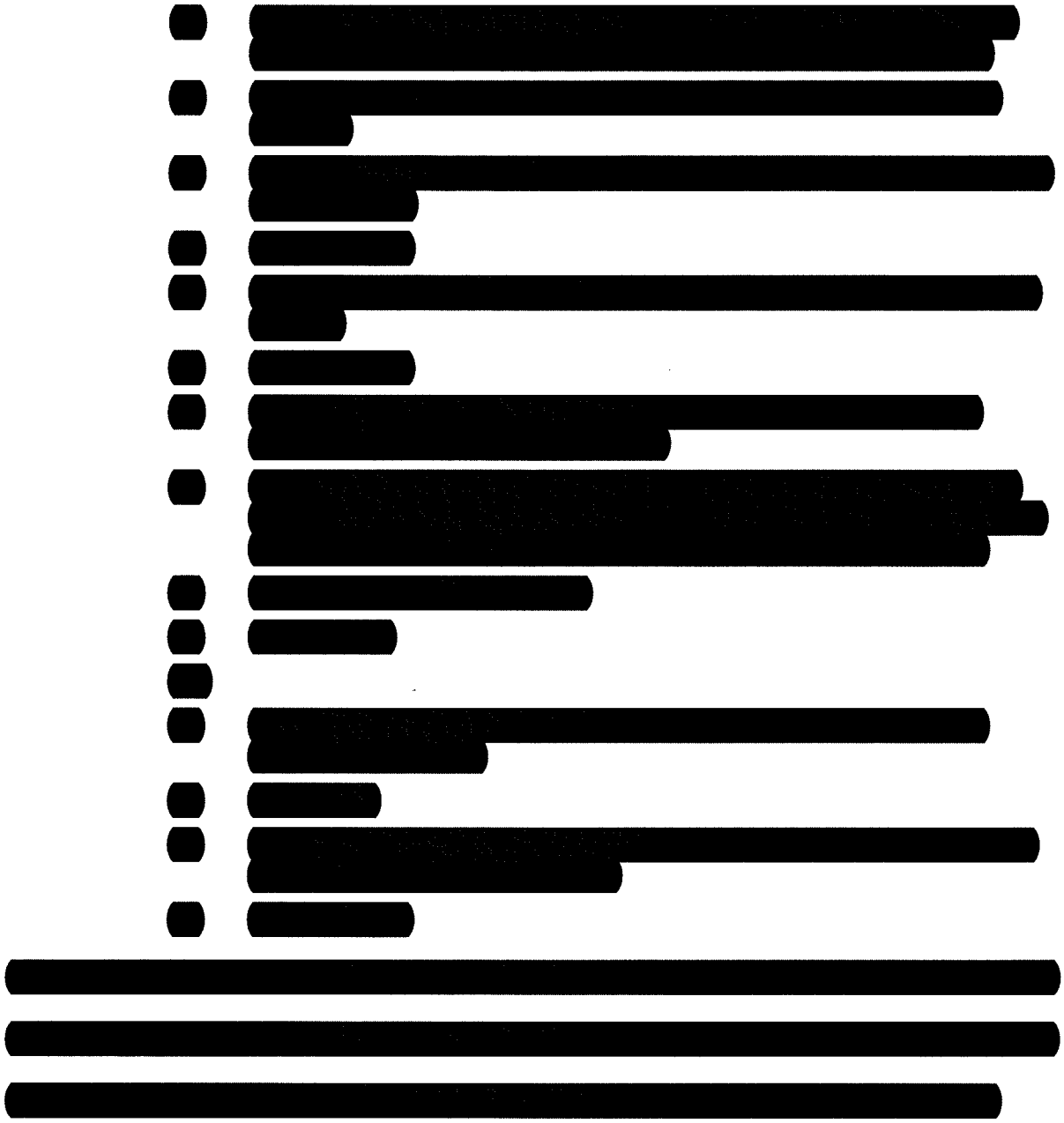
During prosecution, Applicants also relied upon declarations from the inventors and several experts. Duh Decl. Ex. F (4/6/09 Amendment) at 9 (citing Nelson Decl., ¶ 6; Brown Decl., ¶ 10; Beck Decl., ¶ 10; Statham Decl., ¶ 4). The cited portions of the ***inventors'*** declarations do not define the term "imiquimod-related impurities." Duh Decl. Ex. G (Nelson Decl.), ¶ 6 ; Ex. J (Statham Decl.), ¶ 4. While the cited portions of the ***experts'*** declarations use the term "imiquimod-related impurities" and refer to Table 2, they do not offer the opinion that

"imiquimod-related impurities" should be limited to the compounds quantified in Table 2. Duh Decl., Ex. H (Brown Decl.), ¶ 10; Ex. I (Beck Decl.), ¶ 10. Moreover, none of the cited declarations recite a single exemplary "imiquimod-related impurity" that might help to clarify the term. In fact, paragraphs 10 of the Brown and Beck Declarations (which are identical) worsen the ambiguity of the term by referring to the impurities described in Table 2 as "imiquimod degradants and ***related*** imiquimod substances . . . . " Duh Decl., Ex. H (Brown Decl.), ¶ 10; Ex. I (Beck Decl.), ¶ 10 (emphasis added).[5]

B. Even the named inventor and Plaintiffs' hired expert cannot determine whether a given compound is within the scope of the claims.

Neither the named inventor nor the Plaintiffs' hired expert can determine whether a particular substance constitutes one of the claimed "imiquimod-related impurities"; this is further evidence that the term is indefinite. *See, e.g.*, *Amgen*, 927 F.2d at 1218 (finding evidence of indefiniteness in the fact that patentee's partner itself questioned whether certain value was within the claim coverage). During his deposition, Robert Nelson, one of the two named inventors of the '672 patent, testified that [redacted]

[5] In addition, as explained above, the '672 patent is completely silent with regard to "imiquimod-related impurities," and it is thus impermissible to use expert declarations to introduce limitations that are not found in the patent itself. *Default Proof*, 412 F.3d at 1298 ("'Although expert testimony and declarations are useful to confirm that the construed meaning is consistent with the denotation ascribed by those in the field of the art, such extrinsic evidence cannot be used to vary the plain language of the patent document.'").



In fact, Plaintiffs themselves have vacillated regarding what constitutes "imiquimod-related impurities." For example, in Plaintiffs' Disclosure of Asserted Claims and Infringement Contentions (dated July 22, 2010),

[redacted]

[redacted]

The vacillation by Plaintiffs and their own hired expert further shows that whether an impurity is "related" to imiquimod is difficult -- or even impossible -- for one of ordinary skill in the art to determine, even one of alleged ordinary skill who was hired by Plaintiffs specifically to measure "imiquimod-related impurities." It should go without saying that if "imiquimod-related impurities" is unclear even to Plaintiffs, then it is very likely indefinite.

[redacted]

[redacted]

This further means that a compound that Plaintiffs claim is a "known impurity" may have changed over time into a different compound, but that Plaintiffs' hired expert did not discern the change. The likeliest explanation for these changes is that the structures of even allegedly "known impurities" are not necessarily known to one of alleged ordinary skill in the art hired by Plaintiffs themselves. At best, this means that the assay disclosed in the patent and purportedly used by Plaintiffs' hired expert cannot reliably measure the compounds that Plaintiffs believe are "related" to "imiquimod." Both possibilities highlight the ambiguity of Plaintiffs' proposed construction for "imiquimod-related impurities."

C. Plaintiffs' proposed construction is flawed.

Plaintiffs dispute that this term is indefinite. Instead, Plaintiffs have proposed the following construction: "impurities resulting from the degradation of imiquimod or from the manufacturing process that show absorbance when analyzed with a UV detector set at 308 nm." Plaintiffs' proposed construction is flawed not only because it finds no support whatsoever in the intrinsic evidence but also because it exacerbates the term's ambiguity rather than resolves it. Plaintiffs propose limiting the term to compounds that can be detected using a UV detector set at 308 nm. However, as discussed above, the Test Method set forth in the '672 patent does not

explain which molecules that show an absorbance at 308 nm qualify as the claimed "imiquimod-related impurities."[6] For example, some impurities found in the oleic acid component (in addition to the imiquimod) absorb at 308 nm. Potts Decl., ¶ 12. These impurities can affect the results of an HPLC assay with measurements performed at 308 nm. Accordingly, some of the "unknown impurities" reported in the MedPharm reports might have been from the oleic acid component, not the imiquimod, and therefore might not be considered to be "related" to imiquimod at all. The patent offers no guidance as to which compounds that are identified at 308 nm should be considered "imiquimod-related impurities." Therefore, "a person of ordinary skill in the art cannot translate [Plaintiffs'] definition into meaningfully precise claim scope." *Halliburton*, 514 F.3d at 1251.

"Imiquimod-related impurities" is not defined anywhere in the intrinsic record, and it is ambiguous to one of ordinary skill in the art, even to the named inventor and to Plaintiffs themselves. The Applicants had the power of the pen and could have expressly defined this term during prosecution but failed to do so. Plaintiffs now seek inappropriately to give meaning to an indefinite term in an apparent litigation-inspired effort to preserve their claims' validity. Plaintiffs' proposed construction of the indefinite term "imiquimod-related impurities," however, should be rejected for all of the reasons set forth above, and these claims should be found invalid.

V. THE TERM "AT LEAST ABOUT 80% OLEIC ACID" IS INDEFINITE

Claims reciting the term "about" have been found to be indefinite where a person of ordinary skill in the art cannot determine the limits of the claimed invention. *Amgen*, 927 F.2d

[6] In fact, as discussed above, even the named inventor and Plaintiffs themselves cannot determine whether such a molecule constitutes one of the claimed "imiquimod-related impurities" with any level of certainty.

at 1217-18. In *Amgen, Inc. v. Chugai Pharmaceutical Co.*, the Federal Circuit evaluated whether the use of the term "at least about" rendered patent claims indefinite under 35 U.S.C. § 112 ¶ 2. 927 F.2d at 1217-18. There, the claimed invention included claim language limiting the activity of a specific protein to "at least about 160,000 IU per absorbance unit." *Id.* at 1203. During the prosecution of the patent, the patentee added this numeric range after the patent examiner rejected the original claims reciting a specific activity limitation of "at least 120,000" as anticipated by the prior art. *Id.* at 1217-18. In affirming the district court's holding that the term "at least about 160,000" was indefinite, the Federal Circuit emphasized that the imprecise language of the claimed numeric range, the proximity of the prior art to the claimed range, and the relative imprecision in measuring protein activity all "served neither to distinguish the invention over the close prior art . . . nor to permit one to know what specific activity values below 160,000, if any, might constitute infringement." *Id.* at 1217-18. The court found additional support for its holding in both: (1) the failure of the patent specification, the prosecution history, and the prior art to "provide[] any indication as to what range of specific activity is covered by the term 'about'"; and (2) the complete absence of expert testimony regarding the meaning of the term "about" for purposes of the prior art. *Id.* at 1218.

Each of the independent claims of the '672 patent contains the phrase: "wherein the oleic acid component at or prior to formulation of said pharmaceutical cream contains ***at least about 80% oleic acid*** by weight as a fatty acid." Duh Decl., Ex. A ('672 patent), claims 1, 7, 13 (emphasis added). The term "at least about 80% oleic acid" is indefinite, and the claims invalid, for at least the reasons set forth below.

A. Applicants misrepresented during prosecution – and the Examiner relied on that misrepresentation – that "at least about" had been removed from all pending claims.

During the prosecution of the '672 patent, the Examiner issued an Office Action rejecting certain of the claims under 35 U.S.C. § 112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Duh Decl., Ex. E (3/6/09 Office Action) at 2. In particular, the Examiner stated that "the term 'at least about' is indefinite as there is no indication as to what range of specific activity is covered by this terminology." *Id.* In addition, the Examiner rejected all pending claims as obvious. *Id.* at 2-6.

On April 6, 2009, in response to the Examiner's rejection under 35 U.S.C. § 112, second paragraph, Applicants represented that:

> [T]he term "at least" has been removed ***from all pending claims*** to expedite and advance prosecution. In addition, Applicants contend that the term "about" would be readily understood by one of ordinary skill in the art in light of the specification and further in view of the state of the art at the effective filing date of the application. ***Accordingly, Applicants respectfully submit that, in view of the fact that the term 'at least' has been removed, this rejection is improper and moot, and should be withdrawn***.

Duh Decl., Ex. F (4/6/09 Amendment & Response to Office Action) at 16 (emphases added). However, this was not the case. In fact, as part of the same Response, Applicants amended ***every*** independent claim to ***add*** the following limitation: "wherein the oleic acid component at or prior to formulation contains ***at least about*** 80% oleic acid." Duh Decl., Ex. F (4/6/09 Amendment & Response to Office Action) at 2, 4, 5 (emphasis added).

This went completely unnoticed by the Examiner, who relied on Applicants' representation that the term "at least about" no longer appeared in any of the pending claims in withdrawing the indefiniteness rejection:

> Applicants have amended the claims to remove the term "at least" and point to support in the specification that the term "about" is described and understood. The rejection is being withdrawn herein due to Applicants amendments.

Duh Decl., Ex. K (8/28/09 Office Action) at 3. Applicants should not be permitted to benefit from their misrepresentation (and the Examiner's reliance on that misrepresentation). Accordingly, the Examiner's original indefiniteness rejection should stand, and the claims – all of which recite "at least about 80% oleic acid" – should be held invalid as indefinite. Although this is a sufficient basis for finding the claims indefinite, the term "at least about 80% oleic acid" is also indefinite for the additional reasons set forth below.

B. The term "at least about 80% oleic acid" is neither a term of art nor defined by the intrinsic evidence.

The term "at least about 80% oleic acid" is not a term of art and has no meaning to a person of ordinary skill in the art. Potts Decl., ¶ 15. Further, a person of ordinary skill in the art would not have understood the meaning of the term "at least about 80% oleic acid" in the context of the claims, specification, and/or prosecution history of the '672 patent. *Id.* That is, a person of ordinary skill in the art would find no guidance as to the lower bound of the term "***at least about*** 80% oleic acid" anywhere in the intrinsic evidence relating to the '672 patent. *Id.*, ¶¶ 16, 21. For example, a person of ordinary skill in the art would not be able to tell whether the lower bound fell at 75%, 79%, 79.5%, or somewhere else altogether. *Id.*

Nowhere do the claims or specification define the term "about," let alone the term "at least about 80% oleic acid." Instead, the specification merely states (without elaboration):

> Unless otherwise indicated, all numbers expressing quantities, ratios, and numerical properties of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term 'about.'"

Duh Decl. Ex. A ('672 patent) at 7:19-23; Potts Decl., ¶ 16.

Nor does the prosecution history offer any guidance to a person of ordinary skill in the art on how to discern the boundaries of the term "at least about 80% oleic acid." Potts Decl., ¶¶ 16-21. As discussed above, Applicants introduced this limitation for the first time in their April 6, 2009 Amendment and Response to an Office Action. Duh Decl., Ex. F (4/6/09 Amendment & Response to Office Action) at 2, 4, 5 (adding the phrase "wherein the oleic acid component at or prior to formulation contains ***at least about*** 80% oleic acid" to every independent claim) (emphasis added); Potts Decl., ¶ 17.

Applicants represented that "[s]upport for the claim element 'wherein the oleic acid component at or prior to formulation contains at least about 80% oleic acid by weight,' as introduced into independent claims 29, 35, and 41, can be found in the specification of the above-identified application for U.S. patent [US-2007-0123558-A1] in paragraphs 66, 67, and 82." Duh Decl., Ex. F (4/6/09 Amendment & Response to Office Action) at 8. However, none of these paragraphs allows a person of ordinary skill in the art to determine the lower bound of the term "at least about 80% oleic acid." Potts Decl., ¶ 17-21.

Paragraph 66 corresponds to column 7, lines 19-23 of the '672 patent, which was discussed above: "Unless otherwise indicated, all numbers expressing quantities, ratios, and numerical properties of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term 'about.'" Duh Decl. Ex. L (US-2007-0123558-A1) at [0066]; Potts Decl., ¶ 18.

Paragraph 67 corresponds to column 7, lines 24-25 of the '672 patent and merely states: "All parts, percentages, ratios, etc. herein are by weight unless indicated otherwise." Duh Decl. Ex. L (US-2007-0123558-A1) at [0067]; Potts Decl., ¶ 19.

Paragraph 82 corresponds to column 10, lines 19-22 of the '672 patent and states: "For certain embodiments, the oleic acid component contains at least 50%, at least 60%, at least 70% or at least 80% oleic acid. For certain embodiments, the oleic acid component contains at least 80% oleic acid." Duh Decl. Ex. L (US-2007-0123558-A1) at [0082]; Potts Decl., ¶ 20.

A person of ordinary skill in the art would understand "at least" to mean "greater than or equal to." Potts Decl., ¶ 21. Thus, "at least 80% oleic acid" would be understood to mean a value greater than or equal to 80%, "at least 70%" would mean a value greater than or equal to 70%, and so on. *Id*. However, a person of ordinary skill in the art would find no guidance as to the lower bound of the term "***at least about*** 80% oleic acid" in this paragraph (or anywhere else in the specification). *Id.*, ¶¶ 16, 21. For example, a person of ordinary skill in the art would not be able to tell whether the lower bound fell at 75%, 79%, 79.5%, or somewhere else altogether. *Id.* These claims "are not sufficiently precise to permit a potential competitor to determine whether or not he is infringing." *Morton*, 5 F.3d at 1470.

Because a person of ordinary skill in the art cannot discern "the boundaries of the claim based on the claim language, the specification, and the prosecution history, as well as his or her knowledge of the relevant art area," this term should be found indefinite, and therefore invalid. *Halliburton*, 514 F.3d at 1249-50; *Amgen*, 927 F.2d at 1218.

VI. CONCLUSION

For these reasons, Nycomed respectfully request that this Court enter judgment declaring claims 1-20 of the '672 patent invalid as indefinite under 35 U.S.C. § 112, ¶ 2.

Respectfully submitted,

s/ Leda Dunn Wettre

Leda Dunn Wettre
lwettre@rwmlegal.com
Michael J. Gesualdo
mgesualdo@rwmlegal.com
ROBINSON, WETTRE & MILLER LLC
One Newark Center, 19th Floor
Newark, New Jersey 07102
Telephone: 973-690-5400
Facsimile: 973-466-2760

Attorneys for Defendant
Nycomed US Inc.

Of Counsel:

David B. Bassett
Andrew B. Zoltan
Henry Chen
WILMER CUTLER PICKERING HALE AND DORR LLP
399 Park Avenue
New York, NY 10022
(212) 230-8800

William G. McElwain
Amy K. Wigmore
Jamie T. Wisz
WILMER CUTLER PICKERING HALE AND DORR LLP
1875 Pennsylvania Avenue, Northwest
Washington D.C., DC 20006-3642
(202) 663-6000

Christine E. Duh
WILMER CUTLER PICKERING HALE AND DORR LLP
950 Page Mill Road
Palo Alto, California 94304
(650) 858-6000

Attorneys for Defendant
Nycomed US Inc.

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